Ethics of Phase 1 Oncology Studies
Reexamining the Arguments and Data

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DESPITE SUBSTANTIAL IMPROVE-ments in treatments for individual cancers, 50% of people diagnosed as having cancer, more than 550 000 annually in the United States, still die of it.[1] Therefore, research into finding novel therapies for most cancers remains an important national priority. The process of translating basic research into clinical applications that could potentially lead to larger clinical trials and eventually to effective cancer therapies begins with phase 1 oncology studies. Classic phase 1 oncology studies are cohort studies in which patients are treated at increasing doses so researchers can learn about drug toxicities, maximum tolerated dose, and the pharmacokinetics of the drugs, thereby permitting planning for phase 2 studies of efficacy.[2,3]

Two fundamental ethical challenges are frequently raised about phase 1 cancer research: the risk-benefit ratio and informed consent.[4-8] Some suggest that there is little benefit with substantial risks for patients participating in phase 1 oncology studies. Therefore, it seems irrational for patients to participate in such studies. Because patients do participate, critics argue that there must be a problem with disclosure of information to or lack of understanding by research participants.

Are these claims valid? Are phase 1 studies unethical because they are highly risky with little benefit? Are patients who enroll in phase 1 oncology studies uninformed, misinformed, and/or irrational? What are the ethics

Phase 1 oncology trials are critical to improving the treatment of cancer. Critics have raised 2 fundamental ethical challenges about phase 1 cancer research: the paucity of benefits with substantial risks and poor-quality informed consent. Despite 3 decades of controversy about phase 1 oncology research, there is little critical analysis of the arguments or of the data relevant to these questions. Existing but old data reveal that about 5% of patients in phase 1 trials experience shrinkage of their tumor, with a 0.5% mortality rate. In some notable cases, patients in phase 1 trials have been cured or sustained long-term remissions. Limited data suggest that patients in phase 1 trials may have better quality of life than comparable patients receiving supportive care. More important, the risks and benefits of phase 1 trials are not clearly worse than risk-benefit ratios used by the US Food and Drug Administration to approve chemotherapeutic agents for clinical use. The objections based on informed consent are deficiencies of disclosure, understanding, and voluntariness. The available data do not support the claim that disclosure is deficient. Although studies evaluating patient understanding have substantial methodological problems, they demonstrate that more than 70% of patients understand that they may not directly benefit even when they hope they will personally benefit. Finally, a closer look at issues of voluntariness reveals that patients with advanced cancer who participate in phase 1 research may have a different set of values than do critics and are not coerced. Overall, it appears that phase 1 oncology trials satisfy the requirement for a favorable risk-benefit ratio and that patients who enroll provide adequate informed consent.

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of phase 1 oncology research? Despite nearly 3 decades of controversy about phase 1 oncology research, there exists woefully little critical analysis of these ethical arguments[3-6] and the growing empirical data[9-13] relevant to these questions.

Objections Based on the Risk-Benefit Ratio

A common ethical concern regarding phase 1 oncology studies is that they have an inherent unfavorable risk-benefit ratio. What are the benefits?

Meta-analyses of phase 1 trials of anticancer drugs show an overall response rate of about 5%.[14-17] The majority of these are partial responses with only 0.3% to 0.7% being complete responses—that is, cases in which the tu-

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Table 1. Response Rates of Phase 1 Oncology Trials

	Decoster et al,[15] 1990	Estey et al,[14] 1986
No. of research agents evaluated	87	54
No. of patients	6639	6447
Agents with ≥1 objective response, No. (%)	53 (61)	35 (65)
No. (%) of agents with response rate of		
>15%	4 (4.6)	3 (5)
10%-15%	5 (5.7)	5 (9)
5%-10%	18 (21)	11 (20)
<5%	26 (30)	16 (30)
0%	34 (39)	19 (35)

mor completely disappears based on radiological and other diagnostic evaluations. Moreover, no data verify that response rates translate into a longer life or better control of symptoms.

What are the risks? Death from toxic effects in phase 1 studies is rare but possible—0.5%.[15] Although perceptions that nausea, vomiting, and other debilitating adverse effects are common, the overall frequency, severity, and impact on quality of life of these sequelae have been poorly documented. Nevertheless, even if there are no disabilities or serious morbidities associated with phase 1 studies, there are frequent blood draws, radiological evaluations, physician visits, and biopsies, all of which require a substantial commitment of time and resources from the patients and their families. Critics argue that despite limited data, it seems that with such adverse effects and time commitments, quality of life must be compromised.[5,6,18,19]

With a relatively low clinical benefit, a small but definite risk of death, serious but unquantified adverse effects, and substantial time commitment from patients, phase 1 oncology studies seem very unfavorable, making them inherently unethical:

. . . [Phase 1] cancer drug research, for example, may not be performed on terminally ill subjects under these guidelines because there is no reasonable probability that it will benefit the subjects.[18]

Are There Benefits in Phase 1 Oncology Studies?

There are 3 questions surrounding the risk-benefit ratio of phase 1 oncology studies that critics have neglected. Do the risk-benefit data as presented tell the whole story? What criteria should be used to evaluate whether a particular risk-benefit ratio is favorable or unfavorable? Who should decide if a risk-benefit ratio is favorable or unfavorable?

Data on the risks and benefits of phase 1 oncology studies are limited mainly because they are outdated. We searched the MEDLINE database via PubMed for articles published through April 2003 using the exploded Medical Subject Heading terms *clinical trials, phase 1 and neoplasms and meta-analysis and English language*. The latest available meta-analyses of phase 1 studies report on trials published from 1970-1987. While there has been one report of 23 studies of 610 patients from a single institution, there have been no comprehensive meta-analyses published since 1991.[20] The reasons for the absence of more current data are that the National Cancer Institute data exist in multiple databases that do not record information in a uniform format, prior to 1997 the data are not computerized, and the explosion in the number of phase 1 studies conducted in the last decade. Consequently, neither the newer compounds currently being evaluated, such as antibodies, vaccines, immunotoxins, and antiangiogenesis factors, nor improved supportive care measures are reflected in the commonly cited response rate of 5% and mortality rate of 0.5%. Nevertheless, these are the only data on risks and benefits currently available to inform a risk-benefit analysis.

Although meta-analyses of phase 1 studies show an overall response rate of 5%, such aggregate data conceal important information. More than 60% of the

compounds evaluated had at least 1 objective response, which is tumor shrinkage of more than 50% (**TABLE 1**).[14,15] Indeed, more than 30% of the drugs tested had greater than a 5% response rate. While response rate is all that is consistently reported, it is not clearly linked to prolonged life. More important, there have also been cases in which the benefits have been substantial. When initially tested in the 1970s in phase 1 studies, cisplatin for testicular cancer had a response rate of more than 50%, and in a quarter of cases the tumor completely disappeared and was probably cured.[21] Recently, in phase 1 testing, imatinib mesylate for chronic myeloid leukemia demonstrated complete hematologic response rates of 98%, of which 96% lasted beyond 1 year.[22,23] Thus, saying that only 5% of patients respond in phase 1 oncology studies fails to indicate that in some cases substantial clinical benefits and even cures have been achieved.

Furthermore, the designs of most phase 1 trials are intended to minimize toxicity, which, ironically, ensures that the majority of participants are treated at doses that cannot produce responses in human tumors. Indeed, more than 60% of participants in phase 1 oncology studies appear to receive biologically inactive doses.[14] Consequently, participants face little risk but also little chance of benefits. Some investigators have proposed novel design strategies that would allow more patients to be treated at biologically active doses, increasing the chances for a therapeutic response.[2,3,24,25] The response rates in the meta-analyses underestimate potential response rates that could be achieved with these design strategies. Less than 15% of phase 1 studies use these innovative methods, largely because of concern about minimizing toxicities.[2,26]

More important, there may be nonphysical benefits to participation in phase 1 studies. Well-being, especially in very sick and terminally ill patients, is "not merely the absence of disease or infirmity" but includes psychological, social, and other dimen-

sions.[27] Contrary to critics' perceptions, studies indicate that patients may not find the adverse effects experienced in phase 1 studies vexing.[12] We searched the MEDLINE database via PubMed for articles published through April 2002 using the exploded Medical Subject Heading terms *clinical trials, phase 1 and neoplasms/drug therapy and quality of life or activities of daily living or patient satisfaction or neoplasms/ psychology*. The studies we found demonstrated that participating in phase 1 oncology studies may actually improve patients' quality of life compared with the alternative of receiving supportive care.[28-36] Most important, participating in phase 1 studies is not mutually exclusive with symptom management or palliative care. Participating in phase 1 studies and focusing on quality of life are not necessarily—and should not be—inherently incompatible goals; indeed, enhancing quality of life should be one of the goals of phase 1 oncology studies.[37]

Patients with cancer in phase 1 trials may also receive psychological benefit. Daugherty et al[19] reported that 65% of research participants said they believed that they would receive psychological benefit from being in the phase 1 study. For some participants the routine and regular physician contacts reduce psychological distress during a time of great uncertainty.[12,38] For others, it allows them to exercise their willpower in a situation they did not choose. In addition, some also receive comfort from knowing they are helping future patients with cancer.[10,12,19]

[There is] a complex relationship between knowing the reality of their situation (that they had incurable disease) and hoping that there still might be a treatment that would have a positive effect, even cure. . . . Patients do not seem to be harmed by their experience of participating in a phase 1 trial and may experience benefits, albeit not in terms of tumor control.[12]

Although the scientific objectives of phase 1 oncology studies do not include patient benefit, there do appear to be benefits—and greater benefits than those traditionally ascribed by critics—

from participation in phase 1 oncology studies. It would be ironic if critics of phase 1 cancer studies considered only the physical benefits and ignored these quality-of-life and psychological benefits because they want to ensure a quality dying process for terminally ill patients. Nevertheless, a deeper question remains: Are these benefits enough to make the risk-benefit ratio favorable?

What Standard Determines a Favorable Risk-Benefit Ratio?

To determine when a risk-benefit ratio is favorable or unfavorable requires a standard of evaluation, and one appropriate for patients with advanced cancer who will most likely deteriorate and die. What criteria should be used to define a favorable risk-benefit ratio for phase 1 oncology studies?

Surprisingly, no standard has been explicitly articulated. Indeed, determining risk-benefit ratios is one of the most important but least developed areas of determining the ethics of research trials.[39-42] One approach would be to elucidate a standard based on socially accepted determinations of risk-benefit ratios already used for cancer treatments, such as in US Food and Drug Administration (FDA) approval of cancer agents. For example, high-dose interleukin 2 (IL-2) is the only FDA-approved treatment for metastatic renal cell carcinoma. This IL-2 regimen has a response rate of 14% (5% complete responses, 9% partial responses) with a median response duration of 20 months.[43] The possible toxic effects of IL-2 are substantial, including a sepsis-like syndrome requiring judicious use of fluids and vasopressor support to maintain blood pressure while avoiding pulmonary edema from capillary leak. Other chemotherapy treatments, such as topotecan with a 10% response rate for ovarian cancer, have also been approved by the FDA.[44,45] Similarly, irinotecan is approved for the treatment of metastatic colon cancer on the basis of less than 2 months' prolongation of overall survival. Furthermore, gemcitabine is the FDA-approved treatment of choice for

metastatic pancreatic cancer, despite a 5.4% response rate, because of demonstrated quality-of-life benefits.[46] In all these cases, the risk-benefit ratio has been deemed favorable not just for research but for routine clinical care.

For non–terminally ill cancer patients, the use of chemotherapy with limited benefits is also widely accepted, even if debated. For instance, among patients with newly diagnosed stage I breast cancer, for whom 5-year overall survival is greater than 90%, a 2- or 3-drug chemotherapy regimen lasting 4 to 6 months, with its adverse effects, offers an absolute survival benefit of just 1% to 2%.[47,48] Yet the vast majority of women receive such chemotherapy.

The risk-benefit ratio for phase 1 oncology studies is not clearly worse than risk-benefit ratios used by the FDA as a basis for approval of many chemotherapeutic agents and by many non-terminally ill patients in their decision making. For patients in whom all standard therapeutic interventions have failed, a slight chance of therapeutic benefit is not unreasonable. The risk-benefit assessment requires consideration of the available alternatives.

Who Decides What Constitutes a Favorable Risk-Benefit Ratio?

The lack of explicit criteria means that institutional review board (IRB) members frequently rely on their intuitions to determine what constitutes an unfavorable risk-benefit ratio for phase 1 oncology studies.[49] But IRB members tend to be healthy individuals. Substantial data demonstrate that patients facing serious illnesses make very different assessments of their own condition and the risks they are willing to confront compared with healthy individuals. For instance, families consistently overestimate symptoms and underestimate satisfaction and quality of life of sick patients.[50-54] More important, Slevin et al[55] found that patients with cancer were willing to undergo intensive chemotherapy with substantial adverse effects for a 1% chance of cure compared with oncology nurses

who required the drug to produce a 50% chance, physicians who required it to achieve a 10% chance, and the general public who also needed a 50% chance of cure. Healthy IRB members and critics of such studies are likely to view studies with few benefits and greater risks as unfavorable, yet patients might view the same studies as having a favorable risk-benefit ratio.

It has been argued that in considering protocols involving vulnerable populations, such as patients with mental illness, IRBs should include such patients to ensure that their perspectives are represented in deliberations.[56] Consistency suggests that the views of terminally ill cancer patients should inform IRB determinations of risk-benefit ratios for phase 1 oncology studies. Such patients may not be narrowly focused on physical safety and might view risk-benefit ratios more favorably. Indeed, IRBs that include such patients might emphasize alternative study designs using higher doses that increase toxic effects but also may increase the chance of benefits.

Objections Based on Informed Consent

That patients consent to participate in phase 1 oncology studies with possibly unfavorable risk-benefit ratios is, critics argue, indicative of deficiencies in disclosure, understanding, and voluntariness in the informed consent process.[5,7,16,18] First, it is claimed that physicians exaggerate the benefits while minimizing the risks of research participation. As LeRoy Walters was quoted as having said, "Informed consent documents make phase one studies sound like the cure for your cancer."[57]

Although no studies directly document deficient disclosure, exaggeration of benefits, and minimization of risks, critics argue that despite response rates of just 5%, most participants in phase 1 oncology studies are motivated to participate by hopes for stabilization, improvement, or even cure of their cancer (**TABLE 2**).[12,13,19,38] This suggests that patients either are not given accurate information or fail to understand the information they are provided. Critics also argue that researchers may not provide adequate disclosure because they themselves overestimate the potential benefits from phase 1 oncology studies by 3-fold.[8,19] "These exaggerated estimates may represent ignorance, itself a worrisome finding given that the physicians in this study were the ones to invite patients to participate."[58]

Second, critics argue that most terminally ill patients have deficient understanding of the objectives, benefits, and risks of phase 1 research. For instance, in one study 93% of the participants reported understanding most or all of the information given to them about the phase 1 study in which they had agreed to participate, yet only 31% of them were able to state accurately the purpose of phase 1 studies as dose-finding.[9] Another study found that although 90% of patients with cancer who participated in research reported being satisfied with the informed consent process, few understood the potential for incremental risk or discomfort from participating in research and uncertainty of benefits to themselves.[10]

Finally, some argue that even if patients are given accurate information and understand it, they are vulnerable, their judgment is clouded, and they are not to be trusted with their own decision making. Indeed, their decision to participate in such high-risk–low-benefit research is itself indicative of confused judgment. As one critic put it, terminally ill patients who consent to phase 1 oncology studies have "unrealistic expectations and false hopes."[59]

Therefore, instead of being suspicious of experimentation, patients may demand access to experimental interventions as their right. . . . Respecting patient autonomy does not require that we accept demands for mistreatment, torture, or whatever the dying may want.[18]

Is Disclosure Deficient?

Even though informed consent in phase 1 oncology studies may be the most extensively empirically studied area of informed consent, the data are limited (Table 2). We searched the MEDLINE database via PubMed for articles published through April 2002 using the exploded Medical Subject Heading terms *clinical trials, phase 1 and informed consent and English language*. First, even with 10 studies published, fewer than 400 total patients have been interviewed. Second, the studies are of limited size: all but 1 study evaluated 50 patients or fewer in phase 1 studies and all of them were single-institution studies (Table 2). Third, some even combine responses from patients enrolled in phase 1, 2, and 3 oncology studies, making interpretation relevant to phase 1 studies impossible. Most important, by delaying the administration of the survey instrument until days or weeks after the signing of consent, most of these studies actually evaluate recall of information as opposed to the ethically relevant understanding at the time of decision making.[60]

The empirical data on the adequacy of disclosure of information to participants of phase 1 oncology studies are particularly sparse (Table 2). The only study evaluating the substantive content of 272 phase 1 oncology consent forms found that 99% explicitly stated that the study was research and that in 86% this statement was prominent.[61] Furthermore, 92% indicated that safety testing was the research goal. Overall, the mean length of the risks section was 35 lines in contrast with 4 lines as the average length of the benefit section, and 67% of forms mentioned death as a potential consequence of participation in the study while only 5% mentioned cure as a possible benefit. Only 1 consent form indicated that any benefits were expected.

Similarly, no empirical study has shown that physicians do not accurately disclose the risk, benefits, and experimental nature of phase 1 oncology trials. Although physicians may overestimate the response rates in phase 1 studies, they overestimate risks of death even more, by 20-fold.[19,59] More important, as Tomamichel et al[62] reported from recordings of patient-physician interactions, the lack of

known treatments and the investigational nature of the phase 1 oncology study were verbally stated by physicians to patients with cancer in more than 90% of consultations, and the lack of sufficient knowledge of toxic effects of the drug in more than 80%. Two other studies reported similar findings.[13,63] While substantially more data are needed to evaluate the disclosure of information in phase 1 oncology studies, the available data do not support the notion that disclosure either in consent forms or by oncologists is systematically deficient or distorted.

Do Terminally Ill Patients With Cancer Misunderstand?

Asking questions about understanding is very difficult and many subtleties need to be considered. Because there is no gold standard by which to judge the reliability or validity of questions about comprehension they can be judged only on face validity. This places an even greater burden on the investigator to demonstrate that the questions asked are being interpreted and answered by the research participant in the intended manner.

Many of the questions used to assess understanding by participants in phase 1 research are posed primarily from an investigator's perspective rather than the patient's. The questions and interpretation fail to differentiate between 2 aspects of understanding: comprehension—understanding of the factual components of the information—and appreciation—what the information means to a particular person. For example, one study asked "Why did you decide to enter this research trial? (What was your main reason?)"[19] and reported that more than 70% joined hoping for benefit. Many have interpreted the fact that patients primarily partici-

Table 2. Studies Evaluating the Quality of Informed Consent in Phase 1 Oncology Trials*

Source	Sample Size	Methods of Evaluation	Reasons for Participating	Awareness of Study Purpose and Design	Satisfied With Informed Consent Process	Would Participate Again
Rodenhuis et al,[13] 1984	10	Interview 1 week after treatment began	50% Hoped for improvement of their disease; 30% due to family pressure	60%-80% Recalled "experimental," "so far there are only animal studies," "effect uncertain"		
Tomamichel et al,[62] 1995	31	Quantitative and qualitative analysis of taped interviews	59% Possibility of medical benefit		96%	
Itoh et al,[63] 1997	32	Questionnaire after enrollment but before drug administration	19% Treatment benefit; 63% knew maybe no benefit but participated anyway	43% Knew goal was to determine recommended dose	81% Said they understood almost all information given to them	
Yoder et al,[64] 1997	37	Quantitative and qualitative interviews at study entry and exit	70% to get best medical care; 85% for decreased tumor size			100%
Hutchison,[38] 1998	28	Interviews 2-4 weeks after consenting to participate	Majority hoped for benefit		89%	
Cheng et al,[59] 2000	30	Questionnaire after enrollment	60% Expected to benefit			
Daugherty et al,[9] 2000	144†	Interviews within 1 week of receiving drug	73% Sought anticancer response	31% Knew purpose	96%	
Schutta et al, 2000‡	8	Quantitative and qualitative analysis of taped focus group	Hoped for therapeutic benefit			
Joffe et al,[10] 2001	50§	Mailed survey 1-2 weeks after consent		75% Knew trials were done to improve treatment of future patients; 71% knew there may be no medical benefit to themselves	90%	77%
Moore,[12] 2001	15	Pretreatment and posttreatment questionnaire and structured interviews	3 Themes: need to try everything; maintain hope; help others			

*Blank cells indicate that the domain was not asked or evaluated in that study.
†The initial publication by Daugherty et al[19] of 27 patients is included in these 144 patients.
‡Schutta KM, Burnett CB. Factors that influence a patient's decision to participate in a phase I cancer clinical trial. *Oncol Nurs Forum*. 2000;27:1435-1438.
§Survey of patients participating in phase 1, 2, and 3 studies. Of 207 patients, 50 were enrolled in phase 1 studies. The analysis of responses failed to stratify according to phase.

pate for chance of benefit as indicative of a deficiency in comprehension. Yet this interpretation fails to recognize that patients may very well comprehend their limited chance for personal benefit and still hope that they may benefit. As other researchers put it:

[A]lthough subjects were told that fewer than 10% of patients in phase 1 trials experience a tumor response, many of them believed that someone comprised the percentage of patients who experienced a response and that they might "be in the lucky group."[64]

Furthermore, data showing that patients enroll in the hope of benefit from research may reflect a motivation to maintain hope in a difficult situation rather than misunderstanding of the information. For example, although Daugherty et al[19] found that 85% of patients were motivated to participate for possible therapeutic benefit, 78% were either unwilling or unable to state whether they believed they personally would receive benefit from participating in a phase 1 trial. Similarly, Itoh et al[63] found that 63% of surveyed participants did not expect any benefit but wished to participate anyway. Likewise, although Joffe et al[10] concluded that misconceptions about cancer trials are common among trial participants, their data show that 71% of research participants recognized that there may not be medical benefit to themselves and 75% of them reported that the main reason cancer clinical trials are conducted is to improve the treatment of future cancer patients.

Second, questions from prior studies fail to take into account that people retain only the information salient to them, which may not be the same information ethicists and investigators think is important. In purchasing a house, buyers care about information that is narrow and focused, substantially less than the information the attorney describes about how the deed will be recorded or if the bank will sell the mortgage to another bank. Similarly, studies have found that although most patients believed that they understood the information about the phase 1 trial only about a third were

able to state accurately "what are the doctors trying to find out in the phase 1 cancer research trial in which you're enrolled."[19] Interpreting this as reflecting a lack of understanding by participants of phase 1 oncology studies confuses the intent of a phase 1 study and the probability of benefit from a phase 1 study. Phase 1 studies are not designed or intended to produce benefit. Yet what matters to patients is not the therapeutic intent of phase 1 studies but the probability of receiving benefit from them. It is perfectly reasonable that investigators design and intend phase 1 studies primarily to determine toxicity and patients enroll because of a chance of benefit without there being any misunderstanding. Each group may have its own purposes but not be in conflict with one another and may in fact be complementary. If the patient's tumor shrinks it does not adversely affect the purpose of the phase 1 study, and if the trial determines the toxicity it does not thwart the patient's goal of tumor response. Thus, patients' inability to state the purpose of a phase 1 study as a dose-finding trial probably reflects that patients care more about the probability of receiving benefit, the risks, and requirements of the study than about the scientific methodology or the researcher's intent in conducting the study. This interpretation is supported by data showing that 84% of participants reported that they read the consent carefully, 73% considered it an important source of information, but only 37% considered the consent form important to their decision to participate in the phase 1 study.[10]

Third, questions in prior studies evaluating understanding use limited answer choices that force only one primary reason for participating in a phase 1 study. But, like most decisions, there are usually several reasons to do something even if one reason is more important than the others. For example, in their instrument Daugherty and colleagues[19] list 9 reasons that might have been motivations for patients to participate in phase 1 studies. For each reason, a patient could circle "major," "minor," or "not" depending on the role

that reason played in their decision making. Only 33% said helping future people with cancer was a major reason for participating, leading the investigators to conclude that "altruistic feelings appear to have a limited and inconsequential role in motivating participants to participate in these trials." This interpretation fails to capture the multiplicity of motivations that drives the decision making of research participants. Other reasons, such as the need to do something, comfort from the regularity of clinic visits, family circumstances, and having a sense of control, which may contribute but not be the main reason, would not have been detected in prior studies because they were not asked.

Are Patients With Cancer Able to Choose Freely?

Many argue that even if patients with cancer are given full disclosure and understand the information, the fact that some still opt to receive experimental drugs is indicative that their judgment is clouded by their illness and they are unable to make truly voluntary decisions:

Being ill brings with it a multitude of pressures, and a patient suffering from a life-threatening disease may feel as though she has little choice regarding treatment. Physicians should be aware of how vulnerable patients may be to the coercive influence of unrealistic hope, especially those suffering from chronic, life-threatening disorders.[60]

To categorize the choice of patients with advanced cancer to participate in phase 1 studies as inherently coerced is a serious confusion. By definition *coercion* is a credible and strong threat exerted by one person that limits or adversely affects the options another person has available (J.S. Hawkins and E.J.E., unpublished data, 2003).[65,66] Many patients may feel pushed by nature, fate, and their circumstances to enroll. However, being in a situation with limited and difficult choices does not itself constitute coercion.[67] Unless the adverse choice situation was created by another person, the choice made by the patient should not be labeled as co-

erced. Indeed, having poor options can be consistent with making an autonomous or even laudable choice.[64,65]

More important, there are simply no data on the voluntariness of the informed consent process in phase 1 studies. Claims of coercion may be projections rather than empirically substantiated facts. They arise from the view that any clearly thinking person would desire palliative care and being at home with family rather than aggressive chemotherapy at the end of life. But many dying people want chemotherapy, even if there is a very low chance of benefit and a reasonable chance of toxic effects, because it offers them hope or fits with their life narrative to fight against the odds and to overcome challenges; to die without trying everything would be false to themselves and their values. George Zimmer, a professor of English and participant in several phase 1 oncology studies, put it this way:

Letting a patient choose the poisons (under professional guidance) adds something to the will to struggle. We who are struggling to escape cancer do not, obviously, want to die of it. . . . The enemy is not pain or even death, which will come for us in any eventuality. The enemy is cancer, and we want it defeated and destroyed. . . . This is how I wanted to die—not a suicide and not a passively accepting, but eagerly in the struggle.[67]

Vulnerability

Some would argue that even if there is sufficient disclosure, and the patients are making an informed and voluntary decision, they should still not be enrolled in phase 1 studies because they are inherently vulnerable. "We can harm the terminally ill by treating them as objects with nothing to lose. They are our most vulnerable population, and need much more protection than they are currently afforded."[18] Such a claim is faulty. First, the characteristics of patients enrolled in phase 1 research trials are not consistent with what regulations define as a vulnerable population: 88% are white, 57% are male, and more than 50% are college educated.[9] Second, it is unclear what about terminal illness necessarily makes the pa-

tients part of a vulnerable group. Some terminally ill individuals may lack capacity to make decisions because of the effects of illness or medications on their reasoning, but it is unclear why the group as a whole should be considered inherently vulnerable and unable to advance their interests through informed consent.

Most important, even if terminally ill patients are vulnerable, this does not imply an inherent lack of capacity to give informed consent. Estate wills and do-not-resuscitate requests made by terminally ill patients are accepted as genuine; the consent of patients for life-saving organ transplants is not rejected as prima facie invalid because they are made by terminally ill patients who cannot think clearly. The use of "vulnerability" has become a catch-all for many of the ethical issues raised at the end of life. Most people with advanced cancer are able to and do make rational, reasonable, and informed decisions. There will be some individuals who are unable to give adequate informed consent, just as is true for people without advanced cancer. But to conclude that all patients with advanced cancer are, as a group, inherently vulnerable and therefore unable to give informed consent is demeaning.

Conclusion

Phase 1 oncology trials are critical to improving the treatment of cancer. Critics have raised ethical concerns about an unfavorable risk-benefit ratio and informed consent. A critical analysis of the risk-benefit ratio does not show it to be unfavorable. Empirical data on informed consent in phase 1 oncology trials do not support the notion that consent is uninformed.

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